## REMARKS

Favorable consideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 6, 9, 14, 24, 25, 28-34 are under consideration, with claims 6, 14, 28 and 30 being in independent form.

Claims 10, 11, 17-22, 26 and 27 have been cancelled. Claims 6 and 14 have been amended to include language previously recited in cancelled claims 10 and 26, respectively. Claim 24 has been amended to replace reference to cancelled claim 11 with reference to newly added claim 28. Newly added independent claims 28 and 30 are drawn to subject matter previously recited in cancelled claims 11 and 27, respectively. Newly added claims 29 and 31, dependent upon claims 28 and 30, respectively, are drawn to methods wherein the cells are tumor cells. Newly added claim 32, dependent upon claim 30, is drawn to methods wherein the decoy oligonucleotide is selected from the group consisting of: SEQ ID NO: 2 and 11. Newly added claims 33 and 34, dependent upon claims 6 and 14, respectively, are drawn to methods employing anti-sense oligonucleotides having specific SEQ ID NOs. Support for these claims may be found, for example, on page 26, lines 17-19, of the specification as originally filed.

It is urged that support for all the above amendments may be found throughout the specification as originally filed and that none of the above amendments constitute new matter or raise new issues for consideration.

### Rejection under 35 USC §112, first paragraph, Written Description

Claims 6, 9, 14 and 25 stand rejected under 35 USC §112, first paragraph, as lacking an adequate written description. Specifically, the Examiner asserts that the "instant claims encompass the use of any compound that is capable of reducing the amount of a TRA" and that "the specification lacks adequate description of the structure of inhibitors other than antisense or decoy oligonucleotides to YB-1 or its cold shock domain that would be effective in increasing apoptosis". While applicants do NOT acquiesce in this rejection, in order to expedite allowance of applications, the pending claims have been limited to the use of anti-sense or decoy oligonucleotides.

It is urged that one of skill in the art would appreciate that the inventors were indeed in possession of the claimed invention at the time the application was filed, and that the rejection of the claims under 35 USC §112, first paragraph, as lacking an adequate description may thus be properly withdrawn.

**Rejection under 35 USC §112, first paragraph, Enablement**

Claims 6, 9-11, 14 and 25-27 continue to be rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure. Specifically, the Examiner asserts that the specification is only enabling for increasing apoptotic cell death *in vitro* and *ex vivo* in cell culture, and *in vivo* in the mouse. This rejection is respectfully traversed.

In maintaining this rejection, the Examiner appears to be impermissibly requiring that the applicants submit clinical data showing that the claimed methods are effective in increasing apoptosis in human subjects. As discussed previously, and as acknowledged by the Examiner, the instant specification clearly discloses studies both *in vitro* in human cell lines, and *in vivo* in mice, demonstrating that the claimed methods are effective in reducing apoptotic cell death. In the Amendment and Reply dated January 31, 2005, applicants cited several references in which a mouse model was used to demonstrate *in vivo* activity of drugs prior to demonstration of activity in humans. In response the Examiner asserts that "these references do not relate to the YB-1 gene and provide no evidence that inhibition of HER2 would translate to inhibition of the YB-1 gene, not HER2" and further that "Webb et al. discuss an antisense drug to BCL-2 but do not discuss inhibition of YB-1, providing no evidence that similar results can be expected". Applicants wish to stress that these references were not cited as evidence of the activity of antisense or decoy oligonucleotides directed against YB-1, as such evidence is clearly provided in the instant specification. Rather these references were cited to demonstrate that one of skill in the art would reasonably expect the *in vivo* mouse model employed in the instant specification to be predictive of *in vivo* activity in humans.

The courts have stated that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner

has evidence that the model does not correlate (in re Brana 51 F.3d 1560, 1566, 34 USPQ 2s (BNA) 1436, 1441 (Fed. Cir. 1995). Applicants respectfully request that, should the Examiner continue to maintain the present rejection of the claims, she provide evidence clearly demonstrating that the mouse model described in the specification does not correlate with the claimed methods.

It is urged that one of skill in the art, on being provided with the instant specification, would indeed have been able to practice the claimed methods at the time the application was filed, and that this rejection of the claims under 35 USC §112, first paragraph, should therefore be removed.

**Rejection under 35 USC §102**

Claims 6, 9 and 10 continue to be rejected under 35 USC §102(b) as being anticipated by Ohga et al. (Cancer Res. 1996, 56:4224-4228). This rejection is respectfully traversed.

As noted in the previous Amendment and Reply filed on January 31, 2005, Ohga et al. describe studies in which a construct including almost full-length antisense YB-1 was introduced into a human epidermoid cell line called KB in order to establish two stable cell lines having reduced concentrations of YB-1. These cell lines were then shown to have increased sensitivity to various DNA-damaging agents. Ohga et al. do not report observing increased apoptosis on introduction of the antisense YB-1 construct into the KB cells. In the previously filed response, applicants noted that the KB cell line used by Ohga et al. is not a well known line and that therefore the genotype is not generally known, however it appears likely that the KB cell line has a compromised p53 apoptosis pathway. In the present Office Action, the Examiner states that the applicants' arguments were not persuasive "because no factual evidence supporting the assertion that the p53 pathway is compromised in this cell line has been provided". In response, applicants submit the enclosed Declaration of Dr. Annette Lasham, as evidence that one of skill in the art would reasonably conclude, based on the disclosure of Ohga et al. itself, that the KB cell line must have a compromised p53 apoptosis pathway.

It is urged that Ohga et al. neither teach nor suggest the presently claimed methods for increasing apoptosis and that this rejection of claims 6, 9 and 10 under 35 USC §102(b) may be properly withdrawn.

**Concluding Remarks**

A request for a one month extension of time for response to the Office Action is submitted herewith. Every effort has been made to put the pending claims in condition for allowance. Early reconsideration and allowance of the subject patent application is respectfully requested.

Respectfully submitted,

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